· 临床研究 ·

PAX6 新发移码和无义变异导致中国先天性无虹膜病一家系临床表型和基因型分析

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【摘要】　目的　分析先天性无虹膜病一家系的临床表现及其致病原因，并分析候选变异对蛋白结构的影响。　**方法**　采用家系调查研究方法，收集 2023 年 6 月于河南省立眼科医院就诊的中国河南地区汉族先天性无虹膜病一家系 2 代 3 人的临床资料，其中患者 1 例。详细询问患者及其家系成员病史，并进行全面眼科检查，包括视力、眼压、眼前节照相、彩色眼底照相、超声生物显微镜、光学相干断层扫描等。采集该家系成员外周血，对患者进行全外显子组测序，其他成员采用 Sanger 测序验证。对新发现的变异位点进行致病性和蛋白结构分析。　**结果**　先证者男，23 岁，双眼视力较差、无虹膜、角膜变性、晶状体轻度混浊、前房较浅且眼压高、周边视网膜变性、黄斑发育不良。先证者父母临床表型未见明显异常。全外显子组测序显示，*PAX6* 基因外显子 10 存在移码和无义变异 c.734_735del（p.Arg245Asnfs＊20），该变异为第 734～735 位碱基缺失，导致其 245 位精氨酸变异为天冬酰胺，并在其后 19 个氨基酸处提前出现终止密码子。该变异在 HGMD、Clinvar、千人基因组和 gnomAD 数据库均未见收录。先证者父母未携带该变异，符合家系共分离。通过 SMART 工具进行亚结构鉴定发现该变异位于 HOX 结构域中。氨基酸保守性分析发现 *PAX6* 基因翻译的氨基酸序列第 245 位精氨酸在人、小家鼠、家犬、非洲爪蟾、猕猴等物种中高度保守。经 ACMG《序列变异解读标准和指南》评估，该变异被分类为致病性变异（PVS1+PS2+PM2+PP3）。蛋白结构分析显示，PAX6 蛋白的同源结构域和富含脯氨酸-丝氨酸-苏氨酸的结构域缺失。　**结论**　*PAX6* 基因新发移码和无义致病性变异 c.734_735del（p.Arg245Asnfs＊20）是该先天性无虹膜病家系的致病变异位点，该变异使 PAX6 蛋白同源结构域和富含脯氨酸-丝氨酸-苏氨酸的结构域缺失。

【关键词】　无虹膜；家系；移码变异；*PAX6* 基因；基因分析

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Clinical phenotype and genotype analysis of a Chinese family with congenital aniridia caused by a novel frameshift and nonsense variant in *PAX6*

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[**Abstract**]　**Objective**　To analyze the clinical manifestations and explore the etiology in a family with congenital aniridia and to analyze the influence of candidate variants on the protein structure.　**Methods**　A pedigree investigation was performed. A Han Chinese family with congenital aniridia of two generations consisting of three members from Henan Province, including one patient diagnosed with congenital aniridia, was identified and studied following their admission to Henan Eye Hospital in June 2023. A thorough medical history was obtained for the patient and their family members. Comprehensive ophthalmologic examinations were conducted, including visual acuity, intraocular pressure, anterior segment photography, color fundus photography, ultrasound biomicroscopy, and optical coherence tomography, etc. Peripheral blood samples were obtained from the family members and whole exome sequencing (WES) was performed on the patient and validated by Sanger sequencing for other members. The

pathogenicity and protein structure of newly identified variant sites were analyzed. This study adhered to the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Henan Eye Hospital (No. HNEECKY-2023[06]). Written informed consent was obtained from each subject. **Results** The proband is a 23-year-old male presenting with poor binocular vision, aniridia, corneal degeneration, mild lens opacity, shallow anterior chamber, elevated intraocular pressure, peripheral retinal degeneration, and macular dysplasia. The clinical phenotype of the proband's parents did not show any significant abnormality. WES identified a heterozygous frameshift and nonsense varint c. 734_735del (p. Arg245Asnfs * 20) in exon 10 of the *PAX6* gene, which consisited of two bases deletion at positions 734 to 735, resulting in the mutation of its arginine at position 245 to asparagine and the early appearance of a termination codon at the next 19 amino acids. The variant had not been identified in the HGMD, Clinvar, 1 000 Genomes, and gnomAD databases. Neither of the proband's parents carried the variant, consistent with the pattern of family co-segregation. Substructural analysis using the SMART tool indicated that the variant is situated within the HOX domain. Amino acid conservation analysis demonstrated that the arginine residue at position 245 in the *PAX6* gene is highly conserved across multiple species, including human, house mouse, domestic dog, African clawed frog, and macaque. The variant was classified as pathogenic (PVS1+PS2+PM2+PP3) based on the ACMG standards and guidelines for the interpretation of sequence variants. Protein structure analysis revealed the absence of both the homologous domain and the proline-serine-threonine-rich domain in the PAX6 protein. **Conclusions** A novel pathogenic variant, c. 734_735del (p. Arg245Asnfs * 20), in the *PAX6* gene has been identified in a family affected by congenital aniridia. This variant results in the deletion of both the PAX6 protein homology domain and the proline-serine-threonine-rich domain.

[**Key words**] Aniridia; Pedigree; Frameshift variant; *PAX6* gene; Genetic analysis

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先天性无虹膜病是一种罕见的遗传性眼病，发病率为 1/96 000～1/64 000，主要表现为虹膜缺失、眼球震颤、黄斑发育不全、白内障、青光眼、无虹膜相关角膜病和视力严重受损[1-2]。约 13% 的无虹膜病可见于 WAGR 综合征（Wilms 瘤、无虹膜病、泌尿生殖系统异常和智力发育障碍）和 Gillespie 综合征。大部分无虹膜病为常染色体显性遗传，少数为散发病例[3-4]。*PAX6*（11p13，OMIM 607108）基因变异导致的先天性无虹膜病患者占无虹膜病患者的 80%～90%，该基因由 14 个外显子组成（NM_001368894. 2），共 53 种转录本；其编码一种转录调节因子，具有配对结构域和同源结构域 2 个 DNA 结合域，对眼、大脑、脊髓和胰腺发育至关重要[5-6]。截至目前，人类基因突变数据库（Human Gene Mutation Database，HGMD）共记录 *PAX6* 基因 828 种变异，Leiden 开放变异数据库（https://databases. lovd. nl/shared/genes/*PAX6*）报道 289 种 *PAX6* 基因变异，这些变异类型主要为移码、无义或剪接变异等。先天性无虹膜病具有高度的表型异质性，尽管对其发病机制的理解越来越深入，但基因型-表型的关联分析仍具有挑战性[7]。因此，无虹膜病的基因诊断至关重要。本研究拟对先天性无虹膜病一家系的临床表型和基因型进行分析，并分析候选变异对蛋白结构的影响。

1　资料与方法

1.1　一般资料

采用家系调查研究方法，纳入 2023 年 6 月在河南省立眼科医院就诊的中国河南地区汉族无虹膜病一家系。收集该家系成员 2 代 3 人的临床资料，包括 1 例患者（图 1）。本研究遵循《赫尔辛基宣言》，研究方案经河南省立眼科医院伦理委员会批准（批文号：HNEECKY-2023[06]号），所有参与研究的患者及家属均了解本研究目的并自愿签署知情同意书。

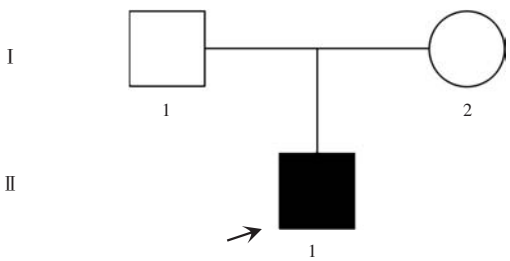

图 1　先天性无虹膜病家系图　□：正常男性；○：正常女性；■：男性患者；↗：先证者

Figure 1　Pedigree of congenital aniridia　□: normal male; ○: normal female; ■: male patient; ↗: proband

1.2　方法

1.2.1　临床检查　详细询问患者及其家系成员病史，

并进行全面眼科检查。采用对数视力表测定受检者裸眼视力和最佳矫正视力；采用裂隙灯显微镜和检眼镜检查眼前节和眼底情况；采用眼科超声生物显微镜（ultrasound biomicroscopy，UBM）（MD-300L，天津迈达医学科技股份有限公司）进行房角检查；采用非接触式眼压计测量眼压；采用超广角扫描激光眼底成像系统（英国 Optos 公司）观察眼底情况；采用光谱域光学相干断层扫描（optical coherence tomography，OCT）（德国 Heidelberg Engineering 公司）评估黄斑结构。

1.2.2　基因检测　采用 IDT xGen Exome Research Panel v1.0 外显子捕获试剂盒（美国 IDT 公司）对外显子区域进行富集，使用 NEBNext Ultra Ⅱ DNA Library Prep Kit（E7645L，美国 NEB 公司）进行文库构建，使用 Illumina NovaseqX plus（美国 Illumina 公司）平台进行 PE 150 bp 测序，测序深度大于 100×，使用 Burrows-WheelerAligner（v0.7.17）软件比对 clean data 与人类参考基因组（GRCh37/HG19），使用 Genome Analysis Toolkit（v4.1.1.0）中 Mutect2 软件进行单核苷酸多态性（single nucleotide polymorphism，SNP）和小片段插入/缺失检测，使用 Annovar（v201804）软件对得到的 VCF 文件进行注释。采用 Sanger 测序验证相关致病性变异及其在该家系成员中的检出情况。

1.2.3　变异致病性分析　将所发现的 SNP 与已知或疑似疾病变异的数据库比对，检索变异位点在 HGMD、Clinvar、千人基因组和 gnomAD 数据库的收录情况。采用 SIFT、PolyPhen-2、LRT 和 Mutation Taster 软件分析候选变异功能，phylop 和 GERP 软件分析变异的保守性，SMART（http://smart.embl-heidelberg.de/）用于模拟基因多肽的拓扑模型。基于美国医学遗传学与基因组学学会（American College of Medical Genetics and Genomics，ACMG）发布的《序列变异解读标准和指南》进行变异分类[8]。

1.2.4　蛋白结构影响分析　依据所得变异构建氨基酸序列，与野生型氨基酸序列比较，使用 AlphaFold2 预测该变异对蛋白三维结构的影响，并采用 PyMOL 2.3 软件进行可视化分析，构建野生型和变异型蛋白三维结构。

2　结果

2.1　临床表现

先证者（Ⅱ-1）男，23 岁，因自幼双眼视力差就诊，既往史无特殊。眼部检查：右眼裸眼视力 0.1，-5.5 DS-2.25 DC×10° = 0.15，左眼裸眼视力 0.1，-6.5 DS-1.25 DC×120° = 0.1；眼压右眼 25.8 mmHg（1 mmHg = 0.133 kPa），左眼 28.4 mmHg；弥散光下眼前节照相检查显示双眼虹膜缺失、晶状体混浊（图 2A）；反照光下照射见双眼角膜变性，角膜缘大量血管翳长入（图 2B）；UBM 检查显示双眼前房深度约 1.8 mm，可见虹膜残端（图 2C）；检眼镜下检查见玻璃体絮状混浊；彩色眼底照相见豹纹状眼底伴视盘周围

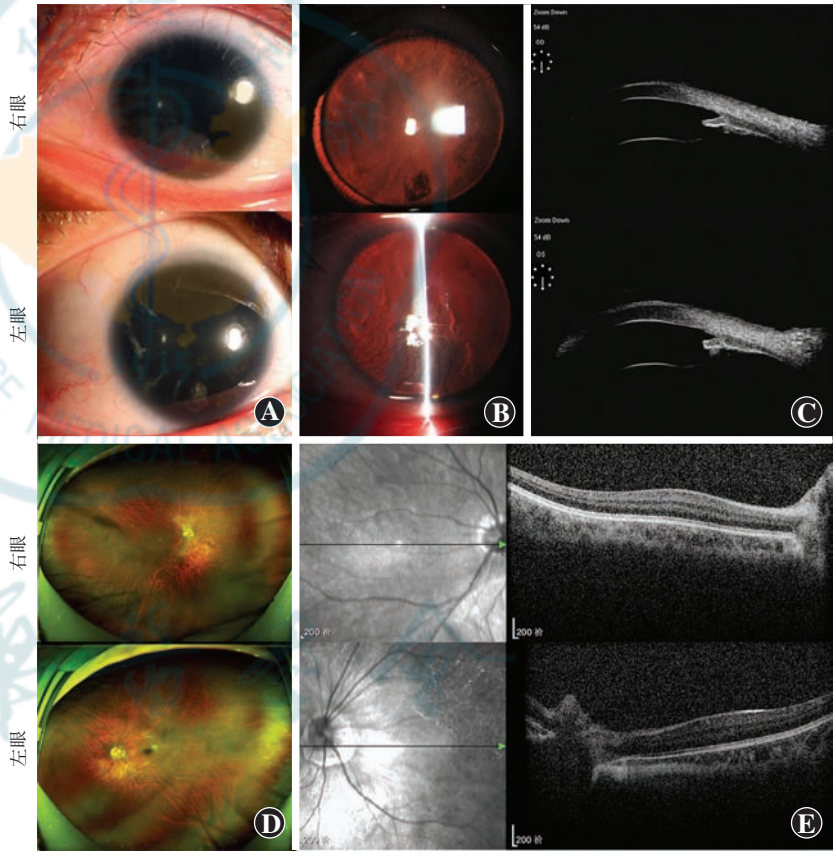

图 2　先证者双眼影像学检查　A：眼前节照相（弥散光）　双眼未见虹膜，晶状体轻度混浊，右眼角膜透明，左眼下方角膜大量血管翳　B：眼前节照相（反射光）　可见双眼角膜缘环周大量血管翳生长，部分长入透明角膜内　C：UBM 检查　可见双眼虹膜残端　D：超广角扫描激光眼底成像　可见豹纹状眼底伴视盘周围萎缩及双眼颞侧周边变性区　E：OCT 检查　可见黄斑区生理凹陷缺失

Figure 2　Binocular imaging results of the proband　A：Anterior segment images（diffuse light）　In both eyes，no iris was seen，and lenses were slightly cloudy. The cornea in the right eye appeared transparent，while a large number of pannuses were seen in the lower cornea of the left eye　B：Anterior segment images（reflected light）　A large amount of pannuses growing around the corneal edge of both eyes were observed，with some extending into the transparent cornea　C：UBM images　Residual iris was seen in both eyes　D：Ultra-wide angle scanning laser fundus images　Symmetrically distributed tessellated fundus accompanied by peripapillary atrophy and temporal peripheral degeneration areas were observed in both eyes　E：OCT images　Physiological depression in the macular region was not observed in both eyes

萎缩及双眼颞侧周边视网膜变性区(图 2D);OCT 检查显示黄斑区生理凹陷缺失(图 2E)。先证者父母相关检查均未见明显异常。

2.2　基因检测

全外显子组测序显示 *PAX6* 基因外显子 10 出现杂合变异 c.734_735del(p.Arg245Asnfs * 20),该变异在 HGMD、Clinvar、千人基因组和 gnomAD 数据库均未见收录,为中等致病性证据(PM2);该变异为第 734~735 位碱基缺失,导致其 245 位精氨酸变异为天冬酰胺,并在其后 19 个氨基酸处提前出现终止密码子,发生移码和无义变异,导致蛋白质翻译提前终止,且该变异不在最后一个外显子,推测可能会发生无义介导的 mRNA 降解,导致基因产物完全缺失而破坏基因功能,为非常强致病性证据(PVS1);表型正常的父母未携带该变异,符合家系共分离,为强的致病性证据(PS2)(图 3);通过 SMART 在线工具进行亚结构鉴定发现该变异位于 HOX 结构域中(图 4)。氨基酸保守性分析发现,*PAX6* 基因翻译的氨基酸序列第 245 位精氨酸在人、小家鼠、家犬、非洲爪蟾、猕猴等物种中高度保守,为支持致病性证据(PP3)(图 5)。经 ACMG《序列变异解读标准和指南》评估,该变异被分类为致病性变异(PVS1+PS2+PM2+PP3)。

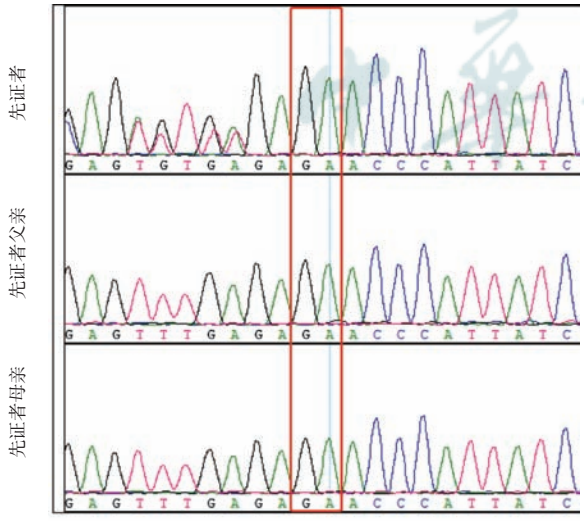

图 3　*PAX6* 变异位点 Sanger 测序图　先证者携带 c.734_735del(p.Arg245Asnfs * 20),其父母未携带,方框内为该位点

Figure 3　Sanger sequencing of *PAX6* variant　The proband carried c.734_735del(p.Arg245Asnfs * 20) and the parents did not. The site was shown in the box

2.3　蛋白结构分析

PAX6 基因 c.734_735del(p.Arg245Asnfs * 20)移码变异后翻译 19 个氨基酸出现终止密码子,该变异导致 PAX6 产生截短蛋白,即 PAX6 蛋白同源结构域和富含脯氨酸-丝氨酸-苏氨酸的结构域缺失(图 6)。

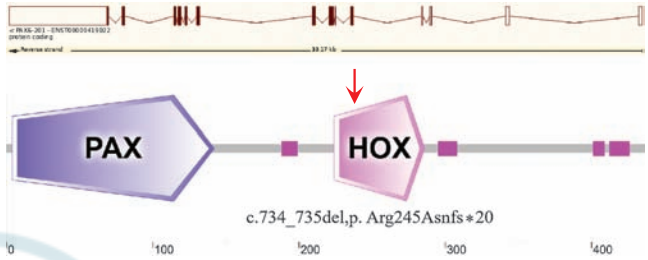

图 4　*PAX6* 变异位点分析　p.Arg245Asnfs * 20 变异位点位于 HOX 结构域中(箭头)

Figure 4　Analysis of *PAX6* variant site　The variant p.Arg245Asnfs * 20 was located in the HOX domain (arrow)

图 5　Arg245 保守性分析　PAX6 蛋白第 245 位精氨酸(方框)在不同物种间高度保守

Figure 5　Arg245 conservation analysis　The arginine at position 245 of PAX6 protein (box) was highly conserved among different species

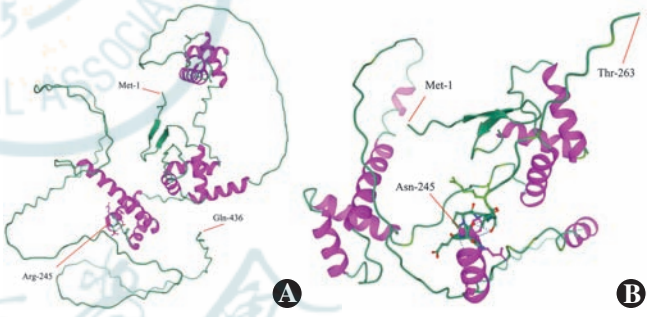

图 6　*PAX6* 基因变异位点 c.734_735del(p.Arg245Asnfs * 20)野生型和突变型蛋白三维模型　A:野生型　B:突变型

Figure 6　Three-dimensional models of wild-type and mutant protein of *PAX6* variant site c.734_735del (p.Arg245Asnfs * 20)　A:Wild-type　B:Mutant-type

3　讨论

先天性无虹膜病患者常表现为视力受损、眼球震颤和中央凹发育不全[9-10],是由于胚胎在发育过程中神经外胚层和中胚层发育障碍导致的眼部结构发育异常[11]。*PAX6* 基因是导致先天性无虹膜病的主要基因。*PAX6* 属于 *Pax* 基因家族,位于 11 号染色体,其编码的转录因子在生物进化过程中高度保守,参与各种组织和器官的胚胎发育,尤其是眼部发育[12]。统计已报道的 *PAX6* 基因变异发现,错义变异占序列变化的 11.7%~17.5%,无义变异占 33%~39%,插入或缺失

移码变异占 19%～25.3%，剪接变异占 14%，框内插入或缺失变异占 0%～6.2%，持续变异占 4.7%～9.5%[13-14]。*PAX6* 基因外显子 8、9、10 和 11 变异占所有变异的 21%，被认为是热点变异区域[15]，且约 1/3 的患者携带变异为新发变异[3]。其中，无义变异、插入或缺失移码变异、剪接变异均可导致蛋白缺失或产生截短蛋白产物，使 *PAX6* 基因单倍体剂量不足，造成眼部组织发育异常，最常表现为虹膜和中央凹发育不全；而 *PAX6* 的错义变异会导致眼前节发育不良和视神经畸形等[16-17]。

本研究在先天性无虹膜病一家系中发现 1 个新发的 *PAX6* 致病性移码和无义变异 c.734_735del，导致 PAX6 蛋白翻译提前终止，单倍体剂量不足；表现为双眼视力较差、无虹膜、角膜变性、晶状体轻度混浊、前房较浅且眼压高、周边视网膜变性、黄斑发育不良，与 *PAX6* 基因变异导致的单倍体功能不全相关的经典无虹膜病表型吻合[18]。该变异位于 HOX 结构域，调控胚胎的早期发育，其活性受损将影响人正常视杯视柄的发育，改变虹膜和睫状体组织的生长和分化，出现无虹膜或虹膜缺损症状[19]。*PAX6* 变异在无虹膜病家系间和家系内均表现出高度的表型异质性，其基因型-表型的关联性仍难以确认。而白内障、青光眼和角膜病等并发症仍是此类患者视力受损的主要原因，目前主要为对症治疗，未来的治疗方向应考虑针对无虹膜病的基因靶向治疗。进行无虹膜病基因检测对于指导受影响个体的临床管理至关重要，尤其是在非典型病例或具有相似表型的疾病中，这些疾病可能导致严重的并发症。由于相关疾病的进展性，无虹膜病患者需要长期监测。

综上所述，*PAX6* 基因新发移码和无义变异 c.734_735del 是该先天性无虹膜病家系的致病原因，该变异诱导了截短蛋白和无效等位基因的产生，导致单倍体剂量不足，虹膜缺失。本研究丰富了 *PAX6* 基因的变异谱系，有助于先天性无虹膜病的遗传学诊断。

利益冲突　所有作者均声明不存在利益冲突

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